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BRUNOVSKIS,P	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/491,974	Applicant(s) Schmaljohn et al.
	Examiner Peter Brunovskis	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☒ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-27* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Objections

Claims 5, 6, 14-16, 21, 26, and 27 are objected to because of the following informalities: In claims 5, 6, and 14-16, "comprises SEQ ID NO:" should be changed to --comprises the sequence set forth in SEQ ID NO:--. In claim 21, "nucleic acid is selected from" should be changed to --nucleic acid comprises a sequence selected from--. In claims 26 and 27, "one or more DNA sequence....the DNA sequence comprising" should be changed to --one or more DNA sequences...wherein said one or more DNA sequences each comprise--. Appropriate correction is required.

Claim Rejections - 35 USC § 101

Claims 2, 6, 8, 15, and 25 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. The specification fails to provide support for using compositions comprising an S gene segment encoding N protein in methods of inducing protective immunity. The specification teaches that "mice vaccinated with pWRG/SEO-S or pWRG7077 by either gene gun or needle inoculation did not develop neutralizing antibodies" (p. 32, lines 10-12) and that hamsters vaccinated with pWRG/SEO-S failed to develop neutralizing antibodies or protect against infection (last paragraph, p. 33 and Table 2, p. 34). The results of the studies employing pWRG/SEO-S were summarized and interpreted to indicate that "[t]he

absence of a neutralizing antibody response in mice and hamsters vaccinated with pWRG/SEO-S, with or without complement, is consistent with published data that monoclonal antibodies to G1 and G2, but not N, have neutralizing activity" (p. 39, lines 13-17).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 9, and 17 (and dependent claims) are indefinite in their recitation of "carrier particle" and "determinant" since it is not clear how these terms are defined or what their metes and bounds are.

Claim 1 (and dependent claims) is indefinite in its recitation of the phrase "DNA sequence coated onto the carrier particle" since a DNA *sequence* has no chemical form to allow coating onto a carrier particle. Deleting "sequence" or changing "DNA sequence" to --polynucleotide [or nucleic acid] coated onto the carrier particle, said polynucleotide comprising a DNA sequence comprising a promoter...--.

Claims 9 and 17 (and dependent claims) is indefinite in its recitation of the phrase "method for inducing a protective immune response" since it is unclear how this phrase is defined or what its metes and bounds are. Specifically, it is is not clear what the term "protection" is directed to: protection from a lethal challenge, protection against a viral infection, etc.

Claim 9, step (i) (and dependent claims) is indefinite in its recitation of the phrase "operatively linked to a promoter" since it is unclear whether this phrase is directed to the hantavirus protein, the determinant, or the nucleic acid.

Claim 9, step (iii) and claim 17, step (iii) (and dependent claims) recite the limitation "the coated carrier particles". There is insufficient antecedent basis for this limitation in the claim.

Claims 9 and 17 (and dependent claims) are indefinite because it is not clear how the phrase "upon exposure to a hantavirus" relates back to either "detecting a protective immune response" or the preamble reciting a method for inducing a protective immune response to a hantavirus infection". For example, it is not clear whether the protective immune response is caused by exposure to the hantavirus or the result caused by accelerating the coated carrier particles into the epidermal cells.

Claim 10 is indefinite in its recitation of the phrase, "wherein the carrier particles are gold" since it is unclear whether the carrier particles are gold in color or whether the form of the carrier particles are gold (i.e. gold [carrier] particles).

Claim 11 recites the limitation "the protein determinant" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 26 (and dependent claims) is indefinite in its recitation of the term "first hantavirus" since no "second hantavirus" is recited in the claim.

Claim 26 (and dependent claim 27) is indefinite because the limitations fail to clearly relate back to a *multivalent* vaccine...comprising *one or more* DNA sequence..." since only one protein coding determinant is recited.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 9, 10, 17-20, 26, and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 9, 10, 17-20, 26, and 27 are drawn to compositions comprising a coding region for a determinant of a hantavirus protein. An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the "determinant" itself. It is not sufficient to define "determinant" solely by its structural relationship to hantavirus, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any "determinant" with a patentably useful biological property. Naming a type of material generically known to

exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular role in protective immunity, for example, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the determinant or nucleic acid encoding it has been isolated. Thus, claiming all "determinants" or their DNAs that achieve a result (i.e. determinant for protective immunity) without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). An adequate description of the methods first requires an adequate description of the "determinants" or specific DNAs encoding them, which provide the means for practicing the invention.

Claim 1- 4, 6, 8, 9, 10, 12, 13, 15, 17-20, 22, 23, and 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions or methods for use in mice or hamsters comprising protein coding region determinants from the M gene segments of the SEOV hantavirus, does not reasonably provide enablement for compositions comprising any other hantaviral protein coding region determinants or for methods of inducing protective immunity against other hantaviruses, except for Hantaan virus and Dobrava virus. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification does not provide sufficient guidance teaching how to use any other compositions, except for those encoding hantaviral M segment proteins.

As discussed above, the specification fails to provide support for using compositions comprising an S gene segment encoding N protein in methods of inducing protective immunity. Since the specification fails to provide support for S gene segments in methods of inducing a protective immune response, and does not provide well-established utility for methods or compositions comprising hantaviral non-M segments for use in the methods of the claimed invention, it fails to provide an enabling disclosure for making and using embodiments comprising any and all hantaviral protein coding region determinants. For example, the specification fails to provide adequate guidance or expectation of success for using any other hantaviral protein determinants in the claimed methods.

Further, the specification fails to provide an enabling disclosure teaching methods of inducing cross-protection against any and all hantaviruses when immunizing with a given M gene segment. The specification teaches the unpredictability of determining a priori which hantaviral M gene segments can protect against which other hantaviruses. For example, although pWRG/SEO-M was shown to be cross-protective in hamsters infected with Hantaan virus (Example 4) or Dobrava virus (Example 5), vaccination with pWRG/SEO-M failed to cross-protect against infection with Puumala virus (Example 6). The specification does not provide any *a priori* basis

for determining which hantaviral M gene segments are capable of protecting against which of the many different hantaviruses.

Additionally, the specification does not provide an enabling disclosure commensurate with using the claimed compositions to induce protective immunity against any and all mammals. At the time the invention was made, it was recognized that vaccine development must involve at least three steps: (i) the identification of the protective effector mechanisms, (ii) the choice of an antigen that can induce a response in all individuals, and (iii) the use of an appropriate way to deliver the vaccine so that it will induce the right type of response (Lanzavecchia, Science, 260:937-944, 5/93). Lanzavecchia further stated that "[t]he distinction between protective, useless, and dangerous responses is essential for vaccine design...[and that] the choice of the antigen, relates to the variability of the host and of the pathogen [and] [t]he capacity to respond to antigen can be influenced by general health, but is mainly determined by genetic MHC-polymorphism. To effectively vaccinate a population, a vaccine must therefore contain epitopes that can be processed and bind to at least one allele in every individual" (p. 938-939). Until a particular combination is prepared and tested in an appropriate animal model, there is no basis for determining or distinguishing a priori those compositions or combinations in accordance with the methods for achieving protective immunity as recited in the instant application.

Part of the problem with enabling the scope of the methods for the broad range of mammals commensurate with the scope of the claimed subject matter, is that "there are no disease models for hantavirus in adult rodents" (p. 32, lines 23-25). It would require undue

experimentation for one of skill in the art to make and test the broad range of constructs in the broad range of mammals to determine patterns of cross-protection against a wide variety of different, distinct, and diverse hantaviruses. However, even if a proper disease model *were* described in the instant specification, the DNA vaccine art had recognized at the time of filing the many difficulties with animal models and their predictive value: .

> "results in mice were not always predictive of those in monkeys and this is likely true for humans as well. Optimal dose and immunization schedule will most likely vary between species. It is not clear whether results in non-human primates will be predictive of results in humans, thus additional studies are required" (McCluskie et al., Mol. Med., 5(5):287-300, 5/99; see abstract).

McCluskie et al. conclude their analysis of the state of the art in stating that:

> "While efficacy in murine models has preceeded the successful development of many human vaccines, it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa. Therefore, it is difficult to predict from mouse studies the potential of a new vaccine for humans. In fact, in those human trails that have been carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors. Furthermore, although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen. We will not know the answer to this until after greater experience has been achieved in non-human primates and human clinical trials" (paragraph abridging p. 296-297).

The specification does not address the problems and unpredictability discussed above and it does not provide adequate guidance teaching one of ordinary skill in the art how to make and use the embodiments of the invention, commensurate in scope with the claimed methods, in the absence of undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 9-13, 15-24, 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmaljohn (Rev. Med. Virol., 4:185-196, 1994) or Chu et al. (J. Virol., 69(10):6417-6423, 10/95), in view of Montgomery et al. (Pharmacol. Ther., 74(2):195-205, 1997), Donnelly et al. (Ann. Rev. Immunol., 15:617-648, 1997), and Arikawa et al. (Virol., 176:114-125, 1990).

Schmaljohn reviews prospects for vaccines to control hantavirus infections. Schmaljohn summarizes the state of the art concerning mechanisms of immunity to hantaviral inventions and discloses that the envelope glycoproteins, G1 and G2 are presumed to be the major elements involved in induction of immunity to hantaan virus (e.g. p. 187, left col.). Schmaljohn further reviews the results of analyses involving recombinant vaccinia virus- or baculovirus-vector candidate vaccines, expressing the entire M segment, portions of the M segment encoding only G1 or only G2, the S segment, or both the M and S segments of HTN virus strain 76-118 wherein 9/9 hamsters immunised once and 4/4 immunised twice with baculovirus recombinants expressing the complete M segment (both the G1 and G2 proteins) were protected from challenge. In contrast, incomplete protection was observed using vaccinia recombinants expressing only G1 or

only G2 and no protection was observed using vaccinia/S segment recombinants. Schmaljohn does not disclose DNA vaccine compositions coated onto carrier particles or methods of their use.

Chu et al. teaches that a vaccinia virus-vectored vaccine expressing the M and S segments of Hantaan (HTN) virus could elicit a protective immune response against other hantaviruses, including other Hantaan and Seoul viruses, but not Puumala virus.

Montgomery et al. reviews the state of the DNA vaccine art and teaches that "[i]f known antigens elicit protective antibodies from a natural infection, results in many disease models support the hypothesis that expression of the antigen from a plasmid will elicit a similar response" (p. 198, left col.). Montgomery further teaches that gene gun delivery of plasmid DNA by adsorption to gold particles offer a convenient and highly sensitive method for achieving humoral and cellular immune responses with as little as 16 ng plasmid in rodent animals (p. 200, left col.).

Donnelly et al. reviews the state of the DNA vaccine art and teaches DNA vaccines offer a simple alternative to other methods involving e.g. live attenuated vaccinia virus recombinants which "may be restricted in use due to concerns about their safety" (p. 619). Donnelly further draw attention to the "remarkable number of publications demonstrating efficacy of DNA vaccines in various preclinical models that have appeared since the publication of the initial demonstration of the generation of protective efficacy attest to the simplicity as well as the robustness of the technology" (p. 620) and discusses the advantage and simplicity associated with being able to alter constructs or mixing different plasmids to explore the use of e.g. different

forms of an antigen or effects of coexpressed cytokines, as well potentially broader, simultaneous protection against different strains and/or antigens by utilizing a combination or "cocktail" DNA vaccine consisting of multiple discrete plasmids encoding several different pathogen antigens or combinations of pathogens to induce a broader spectrum of immune responses from a single preparation (see e.g. p. 625). Donnelly further teaches the benefits of gene gun-mediated DNA vaccine transfer as exemplified by studies comparing the induction of CTL using an influenza NP construct administered epidermally by the gene gun or intradermally by needle injection indicat[ing] that, for this particular construct, injection of 1 μg of DNA i.d. with a conventional needle did not induce CTL whereas as little as 16 ng of DNA did induce CTL by gene gun immunization" (p. 627).

Arikawa et al. discloses the coding properties of the M and S genome segments of the Sapporo rat (SR-11) hantavirus, the etiologic agent of mehorrhagic fever with renal syndrome (HFRS), whose protein coding regions comprise those matching SEQ ID NOs:1 and 2 of the instant application. Arikawa teach that their SR-11 M and S genome segment studies should "provide a basis for the thoughtful development of hantavirus recombinant DNA vaccines and diagnostic reagents" (p. 124, left col.).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to redevelop the vaccinia virus/hantavirus candidate vaccines of Schmaljohn and Chu comprising M and S genome segments by incorporating the teachings of the DNA vaccine art, since Montgomery teaches that a knowledge of antigens found to be important in protective

immunity can be incorporated in the design of DNA vaccines, based on "results in many disease models [which] support the hypothesis that expression of the antigen from a plasmid will elicit a similar response". One of ordinary skill in the art would have been further motivated to combine these teachings in view of the advantages of DNA vaccines over live vaccinia virus vaccines since DNA vaccines are predicted to be safer, easier to maintain, less expensive, and offering greater flexibility, including protection against multiple antigens and/or pathogens as suggested by Donnelly. It would have been obvious to design plasmid vectors encoding M and/or S genome segments coated onto gold carrier particles for gene gun-mediated delivery into the epidermal cells of a mammal, since Montgomery and Donnelly teach the dramatic effects of using small amounts of DNA (cheaper) for gene-gun-mediated delivery into epidermal cells. Design of such vectors, including those comprising the M and S genome segments of SR-11 as suggested by Arikawa in accordance with the cross-protection results of Chu, would have been predicted, with a reasonably high expectation of success, based on the suggestions of Montgomery and Donnelly to have resulted in cheaper, more convenient and potentially more effective vaccines compared to those of Schmaljohn and Chu.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER